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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/555,342	05/26/2000	YUKIO KATO	046124-5025	3974

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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	PAPER NUMBER
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/555,342	KATO ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,17,25,27,32 and 40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15, 17, 25, 27, 32, 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 15, 17, 25, 27, 32 and 40 are being examined.

Claim Rejections - 35 USC § 101, Utility

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 15, 17, 25, 27, 32 and 40 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility, for reasons already of record in paper of 06/09/06.

A. The response asserts that it is unclear to Applicants why claims 15, 17, 25, 27 were rejected for lack of utility under 35 U.S.C 101. The response asserts that these claims were allowed on November 8, 2005 as evidenced by the Notice of Allowance issued by this Examiner, and that Applicants are unaware of any change in the standards for utility under 35 U.S.C. 101 since November 8, 2005.

The response has been considered but is not found to be persuasive for the following reasons:

Although the claims 15, 17, 25, 27 were allowed on November 8, 2005, after review and reconsideration, the claims are rejected under 101, utility because the claims and the specification are not supported by either a specific asserted utility or a well established utility,

for reasons already of record in paper of 06/09/06. The Examiner apologizes for any inconvenience incurred.

B. The response asserts that that the specification provides a detailed discussion as to why CDEP is predicted to be a member of the Rho-GEF family, thereby suggesting that CDEP plays an important role in controlling the adhesion, diffusion, migration, proliferation, and differentiation of cells, including chondrocytes (specification, page 12, lines 1-19; see also pages 33-35). The response asserts that as such, the instantly claimed nucleic acids may be used at the very least to distinguish differentiated cells from non-differentiated or dedifferentiated cells, and particularly differentiated chondrocytes. The response asserts that furthermore, as a gene involved in chondrocyte differentiation, CDEP may be used to induce or maintain the differentiation of chondrocytes (specification page 34, lines 23-24), and that such a use makes it possible to control the differentiated state of chondrocytes playing roles in arthropathies such as osteoarthritis (specification, pages 34-35).

The response has been considered but is not found to be persuasive for the following reasons:

Further experimentation is required to determine whether CDEP plays an important role in controlling the adhesion, diffusion, migration, proliferation, and differentiation of cells, including chondrocytes, because a function of the claimed CDEP protein cannot be predicted, based on sequence homology or sequence motif homology with those of members of the Rho-GEF family, in view of the teaching of Bowie, Burgess et al, Lazar et al, Ofran et al, Skolnick et al, Bork, Barlett et al, Rost et al, all of record. In addition, one cannot determine that the claimed domains of SEQ ID NO:1 are essential for and confer the property of activating Rho protein,

based solely on sequence or domain similarity for the following reasons: Although the specification aligns and compares the amino acid sequences of the claimed domains with the domains erzin, and DH known in the art (the instant figures 3-4), there is no disclosure in the specification, or in the art that the conserved amino acid residues among the different domains known in the art are consensus sequences, which consensus sequences confer and are required for the common activity of the domains erzin, or DH known in the art. There is no disclosure in the specification that the claimed domains contain the consensus sequences of the domains known in the art. The specification only states that there are some percentages of similarity between the claimed domains and the domains known in the art.

Further, although the claimed protein can be used to distinguish differentiated cells from non-differentiated or dedifferentiated cells, and particularly differentiated chondrocytes, the specification does not disclose, nor is it clear what **practical use is for distinguishing differentiated cells from non-differentiated or dedifferentiated cells, and particularly differentiated chondrocytes**.

Concerning the assertion that CDEP may be used to induce or maintain the differentiation of chondrocytes, further experimentation is required to determine whether CDEP protein can induce or maintain the differentiation of chondrocytes. Being expressed in differentiated human chondrocytes would not necessarily confer the ability to induce or maintain the differentiation of chondrocytes, because one cannot predict that the CDEP protein is responsible for inducing differentiation of chondrocytes, or having the same function of activating the Rho protein, as some members of the Rho-GEF family protein, which Rho protein has an important role in

controlling cell differentiation. As such, one cannot predict that the claimed CDEP protein can be used for controlling the differentiated state of chondrocytes in arthropathies such as osteoarthritis

C. The response asserts that in addition, since other Rho-GEF family members are known to become oncogenes as a result of certain N-terminal deletions, CDEP serves as a target for the design of new cancer therapeutics if it shows the same oncogenic potential as other Rho-GEF family members (specification, page 35, lines 3-10).

The response has been considered but is not found to be persuasive for the following reasons:

Although some members of the other Rho-GEF family members are known to become oncogenes as a result of certain N-terminal deletions, further experimentation is required to determine whether the claimed CDEP protein could become an oncogene, because not any protein could predictably become an oncogene, and because there is no correlation between the claimed CDEP protein and cellular proliferation.

D. The response asserts that it is perfectly acceptable to predict a specific utility based on membership in a well-known family of conserved proteins, as the comments accompanying the Utility Guidelines specifically state, such as therapy of osteoarthritis and rheumatoid arthritis, and screening regulators of cell differentiation, which predicted utilities are based on homologies to ezrin, Dbl and pleckstrin. The response asserts that those of skill in the art recognize that sequence homologies make it possible to predict protein structure and function. The response recites Lisa Holm (Current Opinion in Struct. Biol. (1998) 8:372-79, previously submitted), stating that homology is "a most useful concept in computational biology, and that by inferring homology between two proteins on the basis of sequence similarity, biologists can

confidently predict that protein structure and function have also remained similar in evolution" (page 372, col. 1). The response asserts that according to Holm, a "widely used empirical calibration suggested a threshold of 25-30% sequence identity, above which sequence similarity implies structural (and functional) similarity" (page 372, col. 2). The response asserts that further, Applicants have not predicted the Rho-GEF activity of CDEP based on sequence data alone, but also in view of the experimental data reported in the specification, i.e., that CDEP expression is associated with cellular differentiation and changes in morphology, as might be expected for a Rho-GEF protein serving as a regulatory factor for cytoskeleton binding (specification, page 34, lines 5-21).

The recitation of Lisa Holm is acknowledged.

The response has been considered but is not found to be persuasive for the following reasons:

One cannot always predict function of a protein, based on its being a member of a known family. Barlett et al, 2003 (In: Structural Bioinformatics, Bourne et al, eds, Wiley-Liss, Inc., pages 387-407, of record) teach that it is not always that family members will have related functions, as shown by the classic example of divergence of function within the homologous family of lysozyme and alpha-lactalbumin, and as shown by the diverse function of 31 enzyme superfamilies (p.395, item under "Homologous families and function", and p.397, first paragraph). Further, relevant literature reports numerous examples of polypeptide families wherein individual members have distinct, and even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial' cells but not for

vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occuning PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen in vivo, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-/ family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF- beta family members BMP-2 and TGF-beta 1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). Similarly, PTH and PTHrP are two structurally closely related proteins, which can have opposite effects on bone resorption (Pilbeam et a1., 1993, Bone14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

There are, however, some protein families for which assignment of a new protein in that family would convey a specific, substantial and credible utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family. However, this is not the case for the claimed invention as no function has been elucidated for the encoded SEQ ID NO:2 of the claimed invention. There is no indication that the encoded SEQ ID NO:2 could activate the Rho protein. Further, although the encoded

SEQ ID NO:2 contains a domain having some amino acid similarity with an erzin or an Rho-GEF domain, there is no disclosure in the specification, or in the art that the conserved amino acid residues among the different domains known in the art are consensus sequences, which consensus sequences confer and are required for the common activity of the domains.

Further the teaching of Lisa Holme, 1998, is contradicted by the teaching of Bowie, Burgess et al, Lazar et al, Ofran et al, Skolnick et al, Bork, Barlett et al, Rost et al, all of record, many of them are much more recent than that of Lisa Holme. One would reasonably conclude that a function of the claimed CDEP protein cannot be predicted based on sequence homology or sequence motif homology with those of members of the Rho-GEF family, in view of the teaching of Bowie, Burgess et al, Lazar et al, Ofran et al, Skolnick et al, Bork, Barlett et al, Rost et al, all of record.

Concerning the response's assertion that the Rho-GEF activity of CDEP based not on sequence data alone, but also in view of the experimental data reported in the specification, i.e., that CDEP expression is associated with cellular differentiation and changes in morphology, the response is not found to be persuasive for the following reasons:

A function of the claimed CDEP protein cannot be predicted based on sequence homology or sequence motif homology with those of members of the Rho-GEF family, in view of the teaching of Bowie, Burgess et al, Lazar et al, Ofran et al, Skolnick et al, Bork, Barlett et al, Rost et al, all of record, supra. Further, being expressed in differentiated chondrocytes does not confer the ability to induce the differentiation of chondrocytes, because one cannot predict that the CDEP protein is responsible for inducing differentiation of chondrocytes, or having the same

function of activating the Rho protein, as some members of the Rho-GEF family protein, which Rho protein has an important role in controlling cell differentiation.

For the reason set forth above and in previous Office action, the specification and the claims are not supported by a specific, substantial asserted utility. Because the specification and the claims are not supported by a specific, substantial asserted utility, credibility of any utility cannot be assessed.

Claim Rejections - 35 USC § 112 First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15, 17, 25, 27, 32 and 40 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The same arguments and reasons for rejection are set forth above, under 101 utility rejection.

NEW REJECTION BASED ON NEW CONSIDERATION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 15 is rejected under 35 U.S.C. 102(e) as being anticipated by US 6,479,640 (Tonks et al, filed on 05/03/2001, which has as priority date 03/01/1991).

Claim 15 is drawn to: An isolated DNA encoding a protein "having" "an" amino acid sequence as set forth " in" SEQ ID NO: 2.

The language "having" is reasonably interpreted as having the same meaning as the open language "comprising". Further, due to the language "having" and "an", a protein "having" "an" amino acid sequence as set forth " in" SEQ ID NO: 2 encompasses a protein sharing a fragment of SEQ ID NO:2, which could be as small as a few amino acids.

US 6,479640 teaches a polynucleotide, the encoded protein thereof shares several stretches of amino acids with SEQ ID NO:2, as shown by MPSRCH sequence similarity search (MPSRCH search result, 2006, us-09-555-342b-2.p2n.rni, pages 11-13).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SHANON FOLEY can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
February 23, 2007

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